NEW PHARMACEUTICAL COMPOSITIONS CONTAINING AMBROXOL AND ISOPROPAMIDE IODIDE

Related Applications

The priority benefit of EP 02 024 981.0 filed November 8, 2002 and U.S. Provisional Application No. 60/498,406, filed August 28, 03 are hereby claimed, both of which are incorporated by reference herein.

Background of the invention

The present invention relates to novel pharmaceutical compositions comprising as pharmacologically active compounds a combination of an expectorant-effective amount of bromhexine or ambroxol or a pharmacologically acceptable salt thereof and a parasympatholytic (anticholinergic)-effective amount of isopropamide iodide.

The formulation further comprises suitable pharmaceutically acceptable carriers or excipients. Additionally, the present composition may contain other pharmaceutically active compounds.

Another aspect of the present invention relates to methods of using these compositions in the treatment of symptoms of the common cold.
In particular, the inventive composition is useful in the treatment of expectoration and/or runny nose in the many symptoms of the common cold.

Common cold is a condition in which various reactions occur when stimulated by microbes or chilliness to the respiratory organ (also known herein as respiratory tract), and it is an acute inflammation in the respiratory organ, the airway from the mouth and nose through the lungs. More precisely, it is called "common cold syndrome"

Nose inflammation caused by the common cold is called acute rhinitis and brings

about symptoms such as sneezing and runny or stuffy nose. In acute adenoiditis, which is an inflammation of the throat, congestion of the mucous membrane of the throat, swelling, pain and other symptoms occur. When the infection affects the bottom of the respiratory organ, hoarse voice and sometimes dyspnea occur. Once the infection reaches the bronchi, bronchioles, and lungs, onset of cough and sputum begins. In addition to the above-mentioned symptoms in the respiratory organ, headache, fever, low back pain, weariness and anorexia of the whole body appears. Furthermore, gastro-intestinal symptoms including abdominal pain and diarrhea sometimes occur.

Although coldness and allergic reaction are partly attributed to the onset of the common cold, it is often caused by viral infection. The types of viruses that cause the common cold are thought to number more than 200. However, very few drugs are effective against the cold viruses at present. For this reason, symptomatic treatment to control symptoms of common cold such as runny nose, stuffy nose, sneezing, sputum, throat pain, fever and muscle pain is the main pharmaceutical therapy.

However, a drug effective for all symptoms has not been developed yet. Therefore, a combination drug manufactured for each symptom is often used for treatment.

Therefore, it is an objective of the present invention to offer extremely effective pharmaceutical compositions that improve sputum and/or runny nose.

Another objective of the present invention is to offer a medicine for a cold using extremely effective pharmaceutical compositions that improve effectively sputum and/or runny nose among the symptoms of the common cold.

Summary of the Invention

The present invention relates to pharmaceutical compositions comprising a combination of an expectorant-effective amount of bromhexine or ambroxol or a

pharmaceutically acceptable salt thereof and a parasympatholytic (anticholinergic) effective amount of isopropamide iodide. The pharmaceutical compositions further comprise pharmaceutically acceptable carriers or excipients.

The invention further relates to methods of treating various symptoms caused by the common cold, in particular sputum and/or runny nose, comprising administering the pharmaceutical compositions of the invention.

Description of the invention

Thus, it has surprisingly been found that a pharmaceutical composition according to the present invention comprising as pharmacologically active compounds a combination of an expectorant-effective amount of bromhexine or ambroxol or a pharmacologically acceptable salt thereof and a parasympatholytic (anticholinergic)-effective amount of isopropamide iodide, is suitable for treating the symptoms of common cold.

The present invention relates to pharmaceutical compositions comprising as pharmacologically active compounds a combination of an expectorant-effective amount of bromhexine or ambroxol, preferably ambroxol, or a pharmacologically acceptable salt thereof and a parasympatholytic (anticholinergic)-effective amount of isopropamide iodide.

Ambroxol, to be used for pharmaceutical compositions of the present invention, chemical name: trans-4- [2-amino-3, 5-dibromobenzyl] amino] cyclohexanol, is an expectorant classified as a mucosal lubricant drug, which, by the increase in production of pulmonary surfactant, has the effect of lubricating the membrane of the airway. Ambroxol is a metabolite of bromhexine.

In the present invention, preferably ambroxol hydrochloride is used. However, other acid addition salts including hydrobromate, oxalate, nitrate, sulphonate, fumarate, maleate, sulfate phosphate, and the like or freebase can also be used.

In the present invention, bromhexine may be used instead of part or all of the ambroxol.

Bromhexine, to be used for pharmaceutical compositions of the present invention, chemical name: 2-amino-3, 5-dibromo-N-cyclohexyl-N-methylbenzylamine, is an expectorant classified as an airway secretagogue, which has the effect of increasing airway secretion.

In the present invention, preferably bromhexine hydrochloride is used. However, other acid addition salts including hydrobromate, oxalate, nitrate, sulphonate, fumarate, maleate, sulfate phosphate, and the like or freebase can also be used.

In the context of the present invention, bromhexine or its pharmacologically acceptable salt may be blended with the isopropamide iodide in an amount of 1.2 to 32 mg as daily dosage for adults, 8 to 16 mg is more preferable, and 12 mg is most preferable.

In the context of the present invention, ambroxol or its pharmacologically acceptable salt may be blended with the isopropamide iodide in an amount of 5 to 90 mg as daily dosage for adults, 10 to 60 mg is more preferable, and 22.5 to 45 mg is most preferable.

Isopropamide iodide, chemical name: 3-Carbamoyl-3, 3-diphenylpropyl diisopropylmethylammonium iodide, to be used in the pharmaceutical compositions of the present invention is an anticholinergic drug which blocks the parasympathetic nerve and suppresses the excessive secretion of membrane and moderates the runny nose.

The preferred amount of isopropamide iodide is 1 to 25 mg as daily dosage for adults, 2 to 10 mg is more preferable, and 3 to 6 mg is most preferable.

In this present invention, the mixture ratio of isopropamide iodide to ambroxol, preferably in the form of its pharmacologically acceptable salt, e.g. ambroxol hydrochloride, is commonly in the range of 0.01 to 5 weight part. The range is preferably, 0.04 to 1 weight part and more preferably, 0.1 to 0.3 weight part.

The pharmaceutical compositions of the present invention can be administered orally in single or multiple doses. In addition, dosage of ambroxol or its pharmacologically acceptable salt and isopropamide iodide can be adjusted according to age, weight symptom, and the like.

In addition, in the pharmaceutical compositions of this invention, one or more substance(s) selected from the group comprising as pharmacologically active substance antipyretic analgesics, antihistamine, antitussive, stimulant drug, vitamins, crude drug, antacid, mucosa protective as covering materials, antiphlogistic, quenching enzyme and expectorant.

The amount of each of these pharmacologically active substances is decided according to a well-known combination standard in consideration of other kinds and quantity of pharmacologically active substances that are used together.

Examples of antipyretic analgesics are ibuprofen, acetaminophen, ethenzamide, aspirin, aluminum aspirin, isopropylantipyrine, sasapyrine, salicylamide, sodium salicylate, lactyl phenetidine, and the like. They can be used either singly or in two or more combinations. The amount of antipyretic analgesics is commonly 10 to 5000 mg as daily dosage for adults and preferably, it is 225 to 3000 mg.

Examples of an antihistamine agent are isothipendyl hydrochloride, diphenylpyraline hydrochloride, diphenhydramine hydrochloride, difeterol hydrochloride, triprolidine hydrochloride, tripelennamine hydrochloride, thonzylamine hydrochloride, fenethazine hydrochloride, methdilazine

hydrochloride, diphenhydramine salicylate, carbinoxamine diphenyl disulphonate, alimemazine tartrate, diphenhydramine tannate, diphenylpyraline teoclate, mebhydrolin napadisylate, promethazine methylene two salicylates, carbinoxamine maleate, chlorpheniramine maleate, difeterol phosphate, mequitazine, promethazine, cyproheptazine hydrochloride, iproheptine hydrochloride, clemastine fumarate and epinastine hydrochloride, and the like. They can be used either singly or in two or more combinations. The amount of antihistamic agent is commonly 1 to 300 mg as daily dosage for adults and preferably, it is 1.5 to 150 mg.

Examples of an antitussive are alloclamide hydrochloride, hydrochloric acid chloperastine, tipepidine citrate, sodium dibunate, dextromethorphan hydrobromide, dextromethorphan - phenol cover microcosmic salt, tipepidine hibenzate, cloperastine fendizoate, codeine phosphate, dihydrocodeine phosphate, pentoxyverine citrate, noscapine hydrochloride, noscapine, dl-methylephedrine hydrochloride, dl- methylephedrine saccharin salt, carbetapentane citrate, dimemorfan phosphate, benproperine phosphate, isoaminile citrate, oxeladin citrate, oxeladin tannate, eprazinone hydrochloride, clobutinol hydrochloride, clofedanol hydrochloride, fominoben hydrochloride, l-methylephedrine hydrochloride, trimetoquinol hydrochloride, pseudoephedrine, phenylpropanolamine hydrochloride, methoxyphenamine hydrochloride, and the like. They can be used either singly or in two or more combinations. The amount of the antitussive is commonly 2 to 900 mg as daily dosage for adults and preferably, it is 12 to 90 mg.

Examples of stimulant drugs are dl-methylephedrine hydrochloride, dl-methylephedrine saccharin salt, caffeine and sodium benzoate, caffeine, anhydrous caffeine, ephedrine hydrochloride, pseudoephedrine, phenylpropanolamine hydrochloride, phenylephrine, l- methylephedrine hydrochloride, methoxyphenamine hydrochloride, dl- epinephrine hydrochloride, dl- isoproterenol hydrochloride, isoproterenol sulfate, orciprenaline sulfate,

terbutaline sulfate, salbutamol sulfate, trimetoquinol hydrochloride, hexoprenaline sulfate, clorprenaline hydrochloride, tulobuterol hydrochloride, procaterol hydrochloride, pirbuterol hydrochloride, fenoterol hydrobromide, formoterol fumarate, clenbuterol hydrochloride, mabuterol hydrochloride, hydrochloric acid ethylcysteine, methyl cysteine hydrochloride, and the like. They can be used either singly or in two or more combinations. The amount of the stimulant is commonly 1 to 900 mg as daily dosage for adults and preferably, it is 5 to 600 mg.

Examples of vitamins are vitamin B_1 and the derivative and salts thereof such as octotiamine, prosultiamine, fursultiamine, hydrochloric acid fursultiamine, bisbentiamine, benfotiamine, dicethiamine hydrochloride, cycotiamine, cocarboxylase, thiamin disulfide, thiamine hydrochloride, thiamin mononitrate, bisthiamine nitrate, thiamine di- cetyl sulfate salt, bisibuthiamine, and the like, vitamin B_2 and the derivative and salts thereof such as riboflavin, riboflavin tetrabutyrate, riboflavin sodium phosphate, flavin adenine dinucleotide sodium, and the like, vitamin C and the derivative and salts thereof such as ascorbic acid, sodium ascorbate, calcium ascorbate, and the like, hesperidin and the derivative and the salt thereof, vitamin F, vitamin A such as retinol acetate, retinol palmitate and the derivative and the salts thereof, vitamin E and the derivative and salts such as tocopherol, tocopherol succinate, tocopherol calcium succinate, tocopherol acetate, and the like. They can be used either singly or in two or more combinations. The amount of the vitamins is commonly 0.1 to 2000 mg as defined daily dosage for adult and preferably, it is 1 to 500 mg.

Examples of crude drug are crude drug powder and/or the extract such as Ephedra Herb, Nandina Fruit, Cherry Bark, Polygala Root, Glycyrrhiza, Platycodon Root, Plantago Seed, Plantago Herb, Lycoris Radiata Herb, Senega, Fritillaria, Fennel, Philodendron Bark, Coptis Rhizome, Zedoary, Chamomile, Cinnamon Bark, Gentian, Oriental Bezoar, Bear Bile, Glehnia Root, Ginger, Atractylodes Lancea Rhizome, Clove, Citrus Unshiu Peel, Atractylodes Rhizome, Diryu (Earthworm), Panax Rhizome, Ginseng, Scutellaria Root, Pueraria Root, Apricot

Kernel, Cyperus Rhizome, Nonglutinous Rice, Magnolia Bark, Schisandra Fruit, Bupleurum Root, Asiasarum Root, Peony Root, Perilla Herb, Jujube, Ophiopogon Tuber, Pinellia tuber, Poria Sclerotium, Kakkon-to, Keishi-to, Koso-san, Saiko-keishi-to, Sho-saiko-to, Sho-seiryu-to, Bakumondo-to, Hange-koboku-to, Mao-to, Schizonepeta Spike, Forsythia Fruit, Polygala Root, Magnolia, Peach Kernel, Aconite Root, and the like. They can be used either singly or in two or more combinations. The amount of the crude drug is commonly 0.01 to 300 g in extract (converted into raw crude drug) and/or 0.0001 to 60g in powder drug as daily dosage for adults and preferably, it is 0.05 to 30 g in extract (converted into raw crude drug) and/or 0.002 to 6 g in powder.

Examples of antacid and mucosa protectives are aminoacetate, magnesium oxide, magnesium carbonate, magnesium silicate, synthetic aluminum silicate, synthetic hydrotalcite, dihydro aluminum-aminoacetate salt, aluminum hydroxide gel, dried aluminum hydroxide gel, aluminum hydroxide-magnesium carbonate mixing dried gel, aluminum hydroxide-sodium bicarbonate co-precipitate, aluminum hydroxide-calcium carbonate-magnesium carbonate co-precipitate, magnesium hydroxide-potassium aluminum sulfate co-precipitate, magnesium aluminometasilicate and the like. They can be used either singly or in two or more combinations. The amount of antacid and mucosa protective is commonly 10 to 8000 mg as daily dosage for adults and preferably, it is 100 to 4000 mg.

Examples of antiphlogistic and quenching enzymes are bromelain, pronase, serrapeptase, semi- alkali proteinase, streptokinase, streptodornase, lysozyme chloride, tranexamic acid, and the like. They can be used either singly or in two or more combinations. The amount of anti-inflammatory enzyme preparations is commonly 4 to 2000 mg as daily dosage for adults and preferably, it is 15 to 720 mg.

Expectorants, excluding ambroxol, include potassium guaiacolsulfonate, guaifenesin, potassium iodide, foeniculated ammonia spirit, sodium

hydrogencarbonate, bromhexine hydrochloride, fudosteine, carbocysteine, methyl cysteine hydrochloride, acetylcysteine, ethylcysteine hydrochloride, eprazinone hydrochloride, aminophylline, theophylline, diprophylline, proxyphylline, ammonium chloride, cresol potassium sulphonate, l - menthol, trimetoquinol hydrochloride, phenylpropanolamine hydrochloride, methoxyphenamine hydrochloride, and the like. They can be used either singly or in two or more combinations. The amount of expectorant excluding ambroxol is commonly 1 to 3000 mg as daily dosage for adults and preferably, it is 6 to 900 mg.

Pharmaceutical compositions of this invention are used as solid, semi-solid and liquid preparations for oral administration such as tablets, granule, subtle granules, powder, capsule, couplet, soft capsule, pill, suspension, emulsion, liquid, syrup, dry syrup, and the like. Moreover, these preparations may be manufactured after making them into micro particles such as microcapsule, nanocapsule, microsphere and nano sphere.

These preparations can be manufactured according to methods known in the art. Preparation additive may be added to the pharmacologically active substance, if necessary. The manufacture method is not limited.

As an additive to the preparations of the pharmaceutical compositions of this invention, the following can be used including but not limited to: stabilizer, surfactant, plasticizer, lubricant, solubilizer, reducing agent, buffer agent, sweetening agent, base, adsorbent, corrigent, binder, suspension, suspending agent, antioxidant, polish, coating, wetting agent, wet modifier, filler, antifoaming agent, refrigerative agent, coloring matter, flavoring agent, perfume, sugar coating agent, isotonizing agent, softener, emulsifying agent, foaming agent, pH modifier, diluent, excipient, dispersing agent, disintegrator, fragrance, desiccant, antiseptics, preservative, solubilizing agent, solubilizer, solvent, superplasticizer, antistatic agent, extender, moisturizing agent, etc.

Examples of additives include but are not limited to: lactose, sucrose, glucose, mannitol, sorbitol, potato starch, corn starch, wheat starch, calcium carbonate, calcium sulfate, sodium hydrogencarbonate, sodium chloride, microcrystalline cellulose, methyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethylcellulose, sodium carboxymethylcellulose, carboxymethylcellulose calcium, polyvinyl alcohol, magnesium stearate, talc, hydrogenated vegetable oil, macrogol, silicone oil, agar, calcium carbonate, sodium hydrogencarbonate, sodium alginate, shellac, glycerin, aromatic essential oil, water-soluble food dye, rake pigment, benzoic acid, sodium benzoate, para oxybenzoic acid, ester, cationic soap, dehydroacetic acid, boric acid, chlorobutanol, benzyl alcohol, polysorbate 80, fatty acid ester of glycerin, white beeswax, medium-chain triglyceride, ascorbic acid, tocopherol, sodium thiosulfate, sodium edetate, and the like.

For example, when pharmaceutical compositions of this invention are manufactured as tablets, granule, fine granule, powder, capsules, couplet, pill, or dry syrup, in case granulated powders need to be adjusted, the pharmaceutical compositions are manufactured by generally used methods including wet granulation methods such as spray granulation, agitate granulation, flow granulation, roll flow granulation, roll granulation and dry granulation such as compaction granulation. In addition, powders and granulated powders which contain pharmacologically active substance can be mixed and divided into small sachets.

When manufactured as a capsule, the capsule can be filled with powder medicine, granulated powders, small tablets, etc. by using a capsule-filling machine.

Tablets and couplets can be manufactured by mixing powder of the active constituent, powder agent, fine grain agent, granulated powder or pill and additive(s) of the preparation and put to compression molding.

Coated preparations including sugarcoated tablets, couplets, film-coated tablets and coated granulated powder can be manufactured by methods known in the art such as pan coating, flow coating and rolling coating methods and combination of these.

Preparations such as syrup, elixir, limonade, extract, drinkable preparation and soft and hard capsule agents comprising liquid or semi-solid substance are normally manufactured by mixing, dissolving and suspending each pharmaceutically active agent and part of a preparation additive such as a resolvent (e.g. distilled water), adding preparation additive including remaining resolvent and adjusting the volume of liquid. Acid or alkali can be used to adjust pH, as necessary. Furthermore, when a fat-soluble ingredient is included, it may be solubilized, emulsificated and slurred by using a preparation additive such as detergent, solublizing agent, emulsifier and suspending agents. If necessary at preparation, warming, cooling, nitrogen displacement, filtering and sterilization can be performed.

Moreover, functions can be added using preparation additive for: improvement in stabilization, slow release, continuance, quickly distinglation, quickly dissolution and dissolution of medicinal properties, concealment of taste, improvement in usage. Adding these functions can be done by methods known in the art. For example, dispensing pharmaceutically active substance in a separate granule, making multi-layer granules, multi-layer tablets or dry coated tablet, tablets by separating granules, microcapsules, coating preparations such as sugarcoated tablets, film coating tablets, coating granule, foaming pharmaceutical preparation, chewable preparation, dissolving preparation in the mouth, matrix preparation, together comminution, making solid solution, adding sweetening agent, refrigerant, antioxidant or stabilizing agent, adjust to certain pH, viscosity, osmotic pressure, salt concentration. These methods can be combined.

The present invention is further described in the following examples which are

provided for illustrative purposes only and are not to be construed as limiting. Indeed, other variants of the invention will be readily apparent to one of ordinary skill in the art.

All publications and patents cited herein are incorporated by reference in their entireties.

Example 1: Tablet

Tablets were manufactured by evenly mixing the following ingredients. The mixed powder was molded by direct compression to have 120 mg per tablet.

Ambroxol hydrochloride	135 g
Isopropamide iodide	18 g
Lactose	459 g
Crystalline cellulose	450 g
Light anhydrous silicic acid	8 g
Talc	5 g
Magnesium stearate	5 g

Example 2: Powder medicine

A powder was manufactured by evenly mixing the following ingredients. The mixed powder was molded to have 600mg per sachet.

Ambroxol hydrochloride	45 g
Isopropamide iodide	6 g
Acetaminophen	900 g
Corn starch	289 g
Lactose	540 g
Magnesium stearate	20 g

Example 3: Syrup

A total of 240 ml syrup was manufactured by dissolving the following ingredients in distilled water.

Ambroxol hydrochloride	0.15 g
Isopropamide iodide	0.02 g
Acetaminophen	3.00 g
Dihydrocodeine phosphate	0.08 g
dl-Methylephedrine hydrochloride	0.20 g
Chlorpheniramine maleate	0.03 g
Absolute caffeine	0.25 g
Trehalose	120.00 g
Citric acid	0.10 g
Sodium citrate	0.10 g
Caramel	0.10 g
Aroma chemical	0.50 g

Example 4: Sugarcoated tablet

Tablet powder was manufactured with the following ingredients in the usual manner and molded to have 270 mg per tablet.

Ambroxol hydrochloride	90 g
Isopropamide iodide	12 g
Ibuprofen	900 g
Dihydrocodeine phosphate	48 g
dl-Methylephedrine hydrochloride	120 g
Chlorpheniramine maleate	15 g
Anhydrous caffeine	150 g
Thiamine nitrate	48 g

Ascorbic acid	600 g
Corn starch	1257 g
Lactose	936 g
Crystallized cellulose	360 g
Hydroxypropylcellulose	180 g
Light anhydrous Silicic acid	90 g
Talc	36 g
Magnesium stearate	18 g

This tablet was coated in the coating pan, using coating liquid (ethyl alcohol: distilled water = 1: 1) containing 5% by weight hydroxypropylcellulose until the weight per tablet increased by 10 mg. Then, solution containing 2% by weight titanium oxide, 3% by weight calcium carbonate, 1% weight by gum Arabic powder and 60% by weight sucrose was used to coat the tablets until the weight per tablet increased by 180 mg. Afterwards, solution containing sucrose of 60% by weight was used for coating until the weight of one tablet increased by 10 mg.

Example 5: Granule agent

Granules were manufactured using the following ingredients in the usual manner and were packed in a cartridge to have 1300 mg for use as a granule agent.

Ambroxol hydrochloride	90 g
Isopropamide iodide	12 g
Ibuprofen	900 g
Dihydrocodeine phosphate	48 g
Methylephedrine hydrochloride	120 g
Chlorpheniramine maleate	15 g
Anhydrous caffeine	150 g

Thiamine nitrate	48 g
Ascorbic acid	600 g
Corn starch	293 g
D-mannitol	5240 g
Tartaric acid	200 g
Aspartame	40 g
Acesulfame potassium	40 g
Perfume	4 g

Example 6: Tablet

Tablets were manufactured by evenly mixing the following ingredients. The mixed powder was molded by direct compression to have 300 mg per tablet.

Ambroxol hydrochloride	45 g
Isopropamide iodide	6 g
Ibuprofen	450 g
Dihydrocodeine phosphate	24 g
Mequitazine	6 g
Pseudoephedrine hydrochloride	60 g
Theophylline	150 g
Lysozyme chloride	90 g
Anhydrous caffeine	75 g
Fursultiamine	24 g
Riboflavin	12 g
Lactose	443 g
Crystalline cellulose	390 g
Magnesium stearate	15 g
Talc	10 g

Example 7: Tablet

Tablets were manufactured by evenly mixing the following ingredients. The mixed powder was molded by direct compression to have 240 mg per tablet.

Ambroxol hydrochloride	45 g
Isopropamide iodide	6 g
Acetaminophen	900 g
Dihydrocodeine phosphate	24 g
dl-Methylephedrine hydrochloride	60 g
Pseudoephedrine hydrochloride	60 g
Epinastine hydrochloride	10 g
Serrapeptase	15 g
Anhydrous caffeine	75 g
Benfotiamine	24 g
Riboflavin	12 g
Lactose	464 g
Microcrystalline cellulose	430 g
Magnesium stearate	20 g
Talc	15 g

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